

Role of Chelating Agents for Prevention, Intervention, and Treatment of Exposures to Toxic Metals

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The role of chelating agents for the prevention, intervention, and treatment of exposures to toxic metals was the topic of a conference held at the National Institute of Environmental Health Sciences, 22–23 September 1994. The objective of the conference was to review experimental and clinical studies concerned with the effectiveness and potential toxicity of chelating agents used to reduce the body burden of various metals and to identify research needs in the area of chelation. The conference was prompted by emerging evidence that low-level exposures to metals may result in toxic effects not previously recognized. For example, the recent interest in use of chelation as an intervention strategy to reduce blood lead levels followed the awareness that exposure to lead in infants and young children resulting in blood lead levels as low as 10–15 µg/dl may impair cognitive and behavioral development (1). The question increasingly asked is to what degree, if any, does increased excretion of a toxic metal reverse established toxicity? For example, does reduction in blood lead levels reverse the impairment of cognitive and behavioral development in children? Does the process of chelation cause potentially dangerous redistribution of lead to susceptible organs from those less susceptible to lead toxicity? While intervention for toxicity from any metal includes removal from exposure, what are the indications for using chelating agents that enhance excretion of metals?

Complete answers to these questions may not be currently available, but discussion of benefits and problems related to chelation therapy should help identify areas needing further study. The conference participants were asked to share current data and to identify gaps in data necessary to obtain a better understanding of the proper place of chelating agents in the management of metals exposure and toxicity.

Chelation of Lead with EDTA

It was suggested at the conference that the essential characteristics of an ideal lead chelator are 1) the ability to reduce the cellular lead burden in the target cells for lead toxicity, 2) the ability to restore or prevent lead-induced loss of cell function, 3) the absence of adverse effects produced by

interfering with homeostasis and utilization of essential trace elements, and 4) no or little intrinsic toxicity (2).

Historically, the drug of choice in treatment of lead toxicity is EDTA (disodium ethylenetetraacetate) (1,3). The common practice of treating children with high lead exposure (blood lead levels of 70–100 µg/dl) with a combination of EDTA and BAL (British anti-Lewisite, Dimercaprol) is believed to reduce mortality from lead encephalopathy from about 30% to 1 or 2% and is more effective under these circumstances than treatment with EDTA alone. EDTA may not be appropriate for treating low-level lead exposures because it must be given parenterally, and it can be toxic in that it increases excretion of some essential metals. EDTA produces substantial diuresis of zinc and a temporary 30–40% decrease in plasma zinc (4).

The relationship between blood lead concentration and the quantity of lead excreted with EDTA treatment is nonlinear. Arithmetic increases in blood lead are associated with exponential increases in excretion of lead. As blood lead levels decrease, the risk–benefit ratio for EDTA becomes progressively less favorable. The lead-chelate complex is filtered by the renal glomerulus with a biological half-time of 1.5 hr. In subjects with normal renal function most of the lead–chelate complex is excreted within 8 hr, but excretion may take as long as 3 days in persons with renal failure. In children in which exposure to lead is of relatively short duration, the correlation between blood lead and chelatable lead is variable. In adults with remote past exposure, the correlation between blood lead and chelatable lead is poor. A larger fraction of the lead burden in children resides in soft tissues compared to adults. After a single challenge dose of EDTA, lead is excreted largely from blood and soft tissues (5–7). However, a single EDTA treatment does not produce a dramatic decrease in bone lead as measured by L X-ray fluorescence (L-XRF) in children (8,9). K-XRF measurements of bone lead are superior to chelation challenge tests as a marker of long-term lead exposure (5). In adults, bone lead measured by trans-iliac biopsies or by *in vivo* tibial K-XRF correlates well with chelatable lead during long-

term chelation therapy. The upper limit of normal lead-chelate excretion is about 650 µg/day for adults and is comparable to that reported in children when normalized for body mass. In adults with elevated bone lead from chronic lead poisoning, there is decrease in blood, bone, and chelatable lead during long-term chelation. Reequilibration between blood and bone lead takes about 2 weeks (7,10).

EDTA nephrotoxicity as described in earlier literature is not found with the currently available pyrogen-free calcium salt at recommended dosage (<50 mg/kg) (11). Experimental studies of efficacy of EDTA and dimercaptosuccinic acid (DMSA) suggest that the toxicokinetics of lead differ in older animals, and there is less reduction in liver and kidney lead than in younger rats. Excretion of essential trace metals after chelation therapy with EDTA or DMSA is greater in older animals than in younger animals (12).

Chelation of Lead with DMSA

The Food and Drug Administration has recently licensed the drug DMSA (succimer) for reduction of blood lead levels ≥ 45 µg/dl. This decision was based on the demonstrated ability of DMSA to reduce blood lead levels. An advantage of this drug is that it can be given orally. However, there is no information regarding its effectiveness in reversing the clinical effects of low-level lead exposure, including effects on the central nervous system. Interest in using DMSA to treat low-level lead exposure has prompted studies regarding the source of the endogenous lead removed by this drug, its possible redistribution between organs, and whether DMSA increases gastrointestinal absorption of lead, since it is administered orally. Answers to these questions are incomplete. While studies in animals show that DMSA does not seem to redistribute lead into the brain from other organs, there is no consensus as to the effectiveness of DMSA in removal of lead from brain and/or bone (13). One study using stable isotopes of lead suggests that DMSA may enhance gastrointestinal absorption of lead,

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but this may be related to dose, duration of treatment and, of course, the amount of lead in the gut (14).

Results of a clinical trial were presented in which the effectiveness of DMSA in removal of lead from 19 children with blood lead levels of 50–69 µg/dl was compared to treatment of 4 comparable children with EDTA. DMSA decreased blood lead by 61%, whereas in 4 children treated with EDTA, blood lead decreased by 45%. The group of 4 children receiving EDTA was too small to evaluate for statistical significance. However, urinary lead was comparable in the two groups. There is a positive correlation between blood lead levels and half-time elimination of DMSA, suggesting that lead may interfere with renal excretion of DMSA and possibly other drugs. Concomitant antibiotics might slightly decrease the efficacy of DMSA (15).

Most of the DMSA excreted in the urine of humans is in the form of a mixed disulfide in which each of the sulfur atoms of DMSA is in disulfide linkage with a cysteine molecule. There is a small amount of excreted DMSA in which only one molecule of cysteine is in disulfide linkage with DMSA. In an experimental study it was found that synthetic DMSA:cysteine (1:2) mixed disulfide mobilizes and increases the excretion of lead in rats preloaded with lead acetate (16).

The actions of DMSA and EDTA on cellular metabolism of lead have been compared in cultures of osteoclastic bone cells. Both DMSA and EDTA have distinct and complex effects on the cellular metabolism of lead. Both compounds reduce the size of the largest and most stable subcellular pool of lead. However, EDTA increases the size of the most rapidly exchanging Pb^{2+} pool without effecting a significant reduction in the total cellular burden. In contrast, DMSA only slightly increases the intermediate lead pool, but effectively reduces the total cellular lead burden. These experiments indicate that DMSA alters the transfer of lead within cells such that a greater percentage of total cellular lead present in cells is in a readily exchangeable pool. Neither DMSA nor EDTA is particularly effective in restoring lead-impaired cell functions such as protein synthesis, porphyrin synthesis, heme synthesis, and osteocalcin expression, even though cellular levels of lead are diminished (2).

Experimental studies in animals have shown that, because of differences in the toxicokinetics of lead in animals at different ages, older (mature) animals may require larger doses of chelating agent than younger animals to remove a particular amount of lead. Also, EDTA increases

excretion of essential metals, calcium, and zinc, whereas DMSA increases the excretion of copper. Human studies have also shown that excretion of copper, and to a lesser degree zinc, are increased by DMSA administration (4,12,17,18).

Chelation of Lead with D-Penicillamine

Penicillamine has been used to chelate toxic metals including copper (in Wilson's disease) as well as lead, mercury, and arsenic. It has been approved by the FDA for treatment of Wilson's disease, cystinosis, and rheumatoid arthritis but not for lead poisoning, primarily to avoid its misuse in the workplace. Nevertheless, a substantial body of experimental and clinical data exists regarding the pharmacology and utility of penicillamine in both adult and childhood lead poisoning. Experience at the Lead Clinic of the Boston Children's Hospital suggests that D-penicillamine increases excretion of lead with a minimal risk to children with blood lead levels <35 µg/dl. Penicillamine may produce substantial reduction in blood lead levels and less rebound than treatment with DMSA or EDTA probably due to the continuity of the penicillamine treatment. Potential side effects include hypersensitivity reactions, particularly in subjects allergic to penicillin (19).

Effects of Lowering Blood Lead by Chelation

NIEHS is sponsoring a randomized, multicenter clinical trial of about 1300 children under 24 months of age is currently testing the effectiveness of succimer in reversing the slower cognitive and behavioral development in children with blood lead levels between 20 and 44 µg/dl. The trial will be conducted on a double-blind basis, and follow-up of the children will extend for at least 2 years. Other interventions such as home cleanup and nutritional supplementation will be done for all children. Results will not be available for some time (20).

A preliminary study presented at the conference showed that lowering blood lead levels in children does not result in a significant beneficial effect on growth (length or height). However, the study did not involve a control group and did not assess dietary and socioeconomic factors (21).

Chelation of Mercury

Another objective of the conference was to review the effectiveness of drugs for removal of mercury. The two chelating agents that have been most studied for removal of mercury are DMSA and a related drug, 2,3-dimercapto-1-propanesulfonic

acid, (DMPS, dimaval) (22). DMSA and DMPS are chemical analogs of BAL (dimercaprol) and can be administered orally. However, the two drugs are biotransformed differently in humans. More than 90% of DMSA excreted in urine of humans is in the form of a mixed disulfide in which each of the sulfur atoms of DMSA is in disulfide linkage with a cysteine molecule. After DMPS administration, however, acyclic and cyclic disulfides of DMPS are the major metabolites in the urine (23,24). Both DMSA and DMPS increase the urinary excretion of mercury.

Animal studies have shown that DMPS exhibits some organ specificity in the chelation of mercury (25,26). In rats exposed to mercuric chloride or mercury vapor, administration of DMPS increased urinary excretion of mercury and decreased renal mercury content. The increase in urinary excretion was directly proportional to the renal burden of mercury in rats injected with mercuric chloride or exposed to mercury vapor. Thus, DMPS may be of potential use to measure the renal burden of lead and mercury.

About two-thirds of the mercury excreted in persons with mercury-containing dental amalgams appears to be derived from mercury vapor released earlier from their amalgams, and a highly significant positive correlation has been found between numbers and sizes of amalgam fillings and urinary mercury excretion following DMPS administration (27).

In a clinically controlled trial in which half the subjects received DMSA and the other half received a placebo, DMSA increased the urinary excretion of lead, copper, mercury, and, to a lesser degree, zinc in the first 24 hr; lead excretion increased about 10-fold over controls, whereas both copper and mercury doubled. Although DMSA enhances excretion of mercury, lead is the toxic metal most clearly affected by DMSA treatment (17).

While elemental or inorganic mercury can be removed from tissues by chelating agents, it is unlikely that methylmercury can be chelated (28). The methylmercury cation, CH_3Hg^+ , forms a thermodynamically stable bond with the deprotonated thiol group. Thus, the formation of only one bond between mercury atom and another ligand precludes the formation of ring structures needed to produce a metal chelate. However, the strong linear bond formed between mercury and a thiol group allows the formation of a variety of complexes, whereby thiol-containing compounds may be used for antidotal therapy. Exchange with the protein-bound mercurial should be rapid (29), provided that the thiol com-

pound to be used as an antidote can penetrate the macrostructure of proteins to reach the site of the bound mercury.

Metallothionein, a Natural Chelator

Metallothionein (MT) was discovered in 1957 as a cadmium-binding protein in the renal cortex of the horse and is characterized as a low molecular weight (>9000 Da), cysteine-rich, metal-binding protein. Mammalian MT contains 61 amino acids. The protein contains no aromatic amino acids or histidine. Twenty of the 61 amino acids are cysteine, and are arranged in a highly conserved sequence which is observed in vertebrate, invertebrate, yeast, and plant MT. Metals bind to MT in metal-thiolate complexes exhibiting tetrahedral (cadmium, zinc) or trigonal (copper) geometry. Two major isoforms of MT (designated MT I and II) have been identified in most species and are controlled separately by different genes. Humans contain subforms of the two isoforms. Recently, a third isoform (growth inhibitory factor, MT III) has been identified in the brain. The MT molecule is divided into two distinct metal-binding domains. The carboxyl terminal half of the molecule is designated the α -domain and represents amino acids 30–61. It contains 11 cysteinyl residues and binds four atoms of zinc or cadmium or six atoms of copper. The β -domain is the amino-terminal half of MT and contains nine cystinyl residues. This domain binds three ions of zinc or cadmium or six copper ions. MT exhibits numerous biological and physiological functions. It appears to have a role in zinc and copper metabolism. The induction of MT protects organisms from toxic metals such as cadmium. MT also exhibits free-radical scavenging activity. Medically, the induction of intestinal MT by zinc therapy is correlated with normal to negative copper balance in

patients with Wilson's disease. Renal MT induction also protects the intestine against the toxic effects of cisplatin treatment. However, tumor cells that are resistant to electrophilic antineoplastic agents exhibit increased cellular MT levels. Thus, MT may protect some tumor cell types against the effects of certain antitumor drugs (30).

The toxicity of the cadmium-metallothionein complex precludes any consideration of use of this natural metal-ligand for clinical use to enhance excretion of metals.

Chelation of Cadmium

Developing an effective chelation therapy for cadmium is difficult because cadmium is tightly bound to metallothionein in liver and kidney. Cadmium in liver has a long half-life (about 30 years in humans) and is gradually mobilized from liver to kidney, which is considered the critical organ for cadmium toxicity. The cadmium-metallothionein complex is extremely toxic to the kidney (31), and most chelating agents that do remove cadmium from the liver are excreted by the kidney, producing nephrotoxicity. Therefore, the best approach to chelating cadmium from the liver is through bile, before it reaches the kidney. A number of substituted dithiocarbamate compounds with a pair of sulfur atoms that serve as donors to cadmium are the most promising types of chelating agents for cadmium mobilization. Sodium *N*-(4-methoxybenzyl)-D-glucamine dithiocarbamate (MeOBGDTC) is one of the most effective for removing cadmium from liver and kidney. Cadmium is then excreted in bile complexed with MeOBGDTC and glutathione (32,33). Although MeOBGDTC and other similar compounds have been shown to be effective in removing cadmium from tissues of experimental animals with cadmium exposure, efficacy in humans has not been demonstrated.

Selective Removal of Copper Bound to Metallothionein by Tetrathiomolybdate

The affinity of copper for binding to MT is higher than that of zinc or cadmium. However, it has been recently shown that copper can be removed both *in vitro* and *in vivo* by tetrathiomolybdate (TTM) without affecting the other two metals bound to MT. The mechanisms whereby TTM removes copper have been studied in a rat model for Wilson's disease, the LEC rat, which expresses a genetically defective copper-dependent ATPase that regulates copper efflux (34).

TTM appears to remove copper from MT and facilitates excretion by three different reaction pathways. When the amount of TTM (from repeated injections) is less than half the amount of copper bound to MT, TTM appears to remove copper only from cytosolic MT; Zn-MT and apo-MT remain in the cytosol ($\text{Cu,Zn-MT} \rightarrow \text{Cu,Zn-MT/TTM} \rightarrow \text{Zn-MT/apo-MT}$). Copper remaining in the liver is present as a copper-molybdenate-sulfur polymer. A putative dimer, MT-TTM connected by a (TTM)-S-Cu-S-(MT) bridge, is also formed. When TTM is greater than half the amount of copper, the TTM dissociates copper from the MT-TTM complex and copper formerly bound to MT becomes associated with a high molecular weight protein in the cytosol. The copper-molybdenate complex bound to the high molecular weight protein is assumed to be a soluble oligomer complex and is thought to be excreted from the liver. A third pathway for removal of copper from MT by TTM is by facilitating the polymerization of the soluble (Cu-S-MoS₂-S-) polymer to an insoluble (-Cu-S-MoS₂-S) polymer (35).

Conference Presenters

H. Vasken Aposhian, University of Arizona
M. George Cheria, University of Western Ontario
Julian Chisolm, Johns Hopkins University
Thomas Clarkson, University of Rochester
Deborah Cory-Slechta, University of Rochester
Patricia Durbin, University of California-Lawrence Berkeley Laboratory
James Fouts, National Institute of Environmental Health Sciences
Arthur Grider, University of Texas at Austin
Robert Goyer, National Institute of Environmental Health Sciences
John Graef, Boston Children's Hospital
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Joseph Graziano, Columbia University
Mark Jones, Vanderbilt University
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Richard Maiorino, University of Arizona
Mary Ellen Mortensen, Children's Hospital, Columbus, Ohio
Janet Phoenix, National Safety Council
Joel Pounds, Wayne State University
Ken N. Raymond, University of California at Berkeley
Walter Rogan, National Institute of Environmental Health Sciences
John Rosen, Montifiore Hospital
Don Smith, University of California at Santa Cruz
K.T. Suzuki, Chiba University
Richard Wedeen, Medical and Dental College of New Jersey

Design of New Chelating Agents for Removal of Cadmium, Copper, and Actinides

For the design and development of new chelating agents for reducing body burden of metals such as cadmium, copper, and the radioactive actinide elements, Pu(IV), Np(V), and U(VI), specific chemical, physiological, and pharmacological properties must be included in the molecule (36,37). There are various approaches to achieving the appropriate design. One approach is to identify an indicator compound by selective screening of possible candidates. Another approach is to start by identifying the possible ways in which a chelating agent structure can be designed to match the geometric and chemical preferences of the central (toxic) metal ion under consideration. This method is illustrated by the development of chelating agents to mobilize cadmium from its intracellular deposit (38). Compounds in this category include dithiocarbamates, mono- and diesters of *meso*-2,3-dimercaptosuccinic acid.

The design of an improved chelating agent for lead has involved an examination of a series of bidentate ligand functionalities that show some significant affinities or preferences for lead (36). This was followed by the design and synthesis of multidentate ligands based on the coordination properties of Pb²⁺ found in simple natural systems, particularly the low-molecular weight peptides found in plants or other organisms (39). Some of the lead-sequestering agents identified by this approach are the thiohydroamato complexes, and mono- and bis-(hydroxypyridinethione) ligands (40).

Conclusion

In summary, the conference achieved its purpose of highlighting the current patterns of clinical usage of chelating agents as well as the current status of promising experimental drugs. Insights were provided as to how to design new agents.

The conference also brought into focus questions about the effectiveness of currently available drugs. Although drugs in current use are effective in lowering levels of toxic metal in body fluids, there is little information about removal of toxic metals for tissues or reversal of toxic effects. The issues discussed in the conference have provided the basis for identifying the following research needs:

- 1) Determine the sites from which lead is removed during chelation therapy and identify which chelator is most effective in removing lead from the nervous system.
- 2) Determine if intervention with chelating agents enhances the reversal of

functional impairment of cognitive and behavioral development associated with exposure to lead.

- 3) Better characterize essential metal excretion during intervention with chelating agents, particularly DMSA.

- 4) Determine whether orally administered chelating agents enhance absorption of toxic metals from the gastrointestinal tract.

- 5) Determine whether there are advantages to the simultaneous use of multiple chelating agents.

- 6) Perform longer-term experiments on lead-loaded primates to investigate removal of lead from bone. Such information might be useful in devising clinical treatments to remove lead from bone. How do different intervention regimens with or without chelating agents compare in terms of removal of lead from tissues particularly the nervous system and bone? This information might help avoid later problems which arise under circumstances when such lead is remobilized as a result of pregnancy or disorders of bone metabolism such as osteoporosis.

- 7) Develop and clinically test chelating agents for removal of cadmium. Further test the use of DMSA and DMPS for removal of mercury.

- 8) Assess the use of less common toxic metals for effective antagonists. These include thallium, beryllium, and the radioactive actinide metals.

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THE AMERICAN SOCIETY FOR CELL BIOLOGY

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December 9-13, 1995
Washington Convention Center
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EXHIBITS

The commercial exhibits will be open 9:00AM-4:00PM Sunday-Tuesday, December 10-12 and Wednesday, December 13 from 9:00AM-3:00PM. There will be approximately 450 exhibit booths, allowing registrants the opportunity to examine state-of-the-art products and services. The ASCB will provide complimentary refreshments each morning and afternoon in the exhibit hall.

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